Cardiovascular Topics

Magnesium and myocardial reperfusion injury — a study in patients undergoing coronary artery bypass surgery

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Summary

This study examined the effect of various doses of magnesium sulphate on the reperfusion injury in patients subjected to coronary artery bypass surgery. Intravenous magnesium sulphate (0, 2, 4 and 6 g) was administered from the onset of surgery up to the release of the aortic cross-clamp. General haemodynamics, pharmacological support of the circulation, CK-MB fraction and Q-wave changes were monitored. In addition, the incidence and severity of reperfusion ventricular tachycardia or fibrillation were recorded.

A total of 138 patients were successfully randomised into one of the groups. There was no difference in the demographics, general haemodynamics or arrhythmias between groups either before or after surgery.

Results of this study do not support the use of magnesium (as per our protocol) as an effective method of limiting the reperfusion injury after cardiac surgery.

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Cross-clamping the aorta during cardiac surgery results in varying degrees of myocardial ischaemia. Once the cross-clamp is removed, reperfusion of the myocardium introduces the risk of reperfusion injury, which consists of arrhythmias, prolonged reversible myocardial dysfunction (stunning) and accelerated cell death.[1] A current and popular view of the pathophysiology of the reperfusion injury is that free oxygen radicals are initially formed, with subsequent intracellular calcium overload.[2-4] Whether this is the only explanation for the reperfusion injury and whether this sequence is necessarily the final and correct one, is still uncertain. However, drugs which antagonise the free oxygen radicals or limit intracellular calcium overload, attenuate the reperfusion injury.[5-7]

Magnesium has been termed 'nature's calcium antagonist',[8] and experimental studies have shown that increasing the magnesium concentration before initiation of reperfusion decreases myocardial stunning,[9] while animals fed a magnesium-poor diet demonstrated increased myocardial stunning once reperfusion occurred.[10] Our own study on the effect of magnesium on the reperfusion injury in an open-chest porcine model also demonstrated beneficial effects if magnesium was administered before reperfusion.[11] When magnesium was administered after myocardial infarction in humans, a large clinical study demonstrated beneficial effects.[12] However, a subsequent study failed to confirm the initial results.[13]

The aim of this study was to evaluate the effect of magnesium on the reperfusion injury when administered before initiation of reperfusion. For this we chose the human model of aortic cross-clamping during cardiac surgery. Based on

the known pathophysiology and animal experiments, our hypothesis was that magnesium should have beneficial effects on the reperfusion injury.

Methods

Permission for the study was obtained from the Ethics Committee of the Faculty of Medicine at the University of Stellenbosch and informed consent was obtained from the patients before surgery.

One hundred and forty-two consecutive patients scheduled to undergo artery bypass surgery (CABG) were enrolled in the study. Only patients with New York Heart Association (NYHA) grade IV for dyspnoea were excluded.

Patients were seen the day before surgery and premedication consisted of morphine 0.1 mg/kg and promethazine (Phenergan) 0.4 mg/kg. They continued with their chronic treatment until the morning of surgery.

In the anaesthetic suite an ECG was attached and intravenous and intra-arterial lines were inserted under local anaesthesia. A central venous pressure (CVP) line or pulmonary artery catheter was inserted via the internal jugular vein.

Beta-adrenergic blockade was instituted with either acebutolol 0.2 mg/kg - 0.5 mg/kg, or esmolol 100 - 500 μg/kg/min unless contraindicated. Glycopyrrolate was given (0.01 mg/kg) intravenously thereafter.

While breathing oxygen, a fentanyl or sufentanil infusion was started, using a target-controlled schedule with a computer-driven syringe (Stelpump, Professor Johan Coetzee and Mr Ralph Pinna, Department of Anaesthesiology and Central Electronic Services, University of Stellenbosch). The target for fentanyl was 5 ng/ml and sufentanil 2 ng/ml. Induction of anaesthesia was completed with etomidate 0.2 mg/kg or thiopentone 2 - 3 mg/kg. Muscle relaxation was obtained with vecuronium 0.1 mg/kg, whereafter endotracheal intubation was performed and the patient was ventilated with oxygen (50%) and air to a normal end-tidal carbon-dioxide tension.

The patient's temperature and urine output were monitored. Maintenance fluid consisted of Ringer's lactate and hetastarch in volumes adjusted to meet the patient's clinical and haemodynamic needs.

Dobutamine 5 - 20 μg/kg/min or adrenaline 0.05 - 0.1 μg/kg/min and nitroglycerin 0.25 - 1.0 μg/kg/min were given as required to maintain the haemodynamics within 75% of awake pre-operative values.

Patients received heparin (2 mg/kg) and the activated clotting time (ACT) used to maintain the ACT between 400 and 500 seconds. At the end of bypass heparin was reversed, using protamine sulphate approximately 1.3 times the total dose of heparin, or until the ACT was within 10% of the pre-operative value.

Once bypass was started, the left ventricle was vented via a pulmonary vein and the aortic cross-clamp applied. The cardioplegic solution was infused into the aortic root (St Thomas II solution gassed with oxygen and kept at 10°C) until asystole was achieved. Thereafter cardioplegia was infused every 20 minutes. Topical cooling of the heart was also performed. The patient was cooled to 28°C for the duration of surgery, and the alpha-stat (uncorrected for temperature) method of blood gas interpretation was used during hypothermia.

Once revascularisation was completed, patients were rewarmed to a nasopharyngeal temperature of 35 - 36°C. Bypass was then terminated and the patient's circulation supported as clinically indicated.

Patients were ventilated postoperatively for 4 - 12 hours depending on the cardiovascular and pulmonary status.

For the purpose of this study, the following were recorded: (*i*) the patient's demographic data, chronic medication, as well as cardiovascular status and other cardiovascular risk factors; (*ii*) systolic, diastolic and mean arterial blood pressure (SAP, DAP, MAP); (*iii*) heart rate (HR); (*iv*) central venous pressure (CVP); (*v*) aortic cross-clamp time (minutes); (*vi*) defibrillation required after unclamping the aorta (joules); (*vii*) lignocaine required after aortic unclamping (mg/kg); (*viii*) phenylephrine required after bypass (mg/kg for the duration of the operation); (*ix*) blood magnesium concentra-

TABLE I. DEMOGRAPHICS, CARDIOVASCULAR STATUS AND PRE-OPERATIVE TREATMENT OF STUDY GROUPS (MEAN ± SD)

		Groups			
	Total	*O g $MgSO_4$*	*2 g $MgSO_4$*	*4 g $MgSO_4$*	*6 g $MgSO_4$*
N	138	31	37	40	30
Age (yrs)	58.5 ± 11.8	60.2 ± 10.9	56.1 ± 12.3	61.4 ± 10.5	55.9 ± 12.4
Men/women	105:33	24:7	32:5	23:17†	26:4
BSA (m^2)	1.9 ± 0.2	1.9 ± 0.2	1.8 ± 0.2	1.9 ± 0.5	1.9 ± 0.2
Hypertension (%)	51	51	33	63	53
Diabetes (%)	18	22	11	25	16
Angina class*	2.7 ± 0.8	2.7 ± 0.9	2.8 ± 1.2	3.0 ± 1.2	3.0 ± 0.8
Exercise class*	2.1 ± 0.6	2.0 ± 0.7	2.3 ± 0.9	2.5 ± 0.9	2.4 ± 0.7
Orthopnoea (%)	23	12	11	30‡	27‡
ß-blocker (%)	90	96	83	82	100
Calcium antagonist (%)	54	48	67	63	66
Nitrates (%)	83	51	81	92	83
Digitalis (%)	7.2	3	16	10	3
Cardiac failure (%)	3.6	3	0	8	0
New Q-waves (%)	33	25	37	32	36

* New York Heart Association class.
†$\chi^2 P = 0.033$.
‡$\chi^2 P = 0.035$.

TABLE II. CARDIOPULMONARY BYPASS AND AORTIC CROSS-CLAMP TIMES AND TREATMENT OF VENTRICULAR FIBRILLATION (MEAN ± SD)

	Groups			
	0 g $MgSO_4$	*2 g $MgSO_4$*	*4 g $MgSO_4$*	*6 g $MgSO_4$*
N	31	37	40	30
CPB time (min)	95.5 ± 38.20	100.1 ± 31.2	100.1 ± 33.0	106.9 ± 36.0
Aorta clamp time (min)	52.1 ± 17.3	56.5 ± 17.0	54.8 ± 16.0	60.3 ± 22.9
Defibrillation (J)	41.9 ± 37.6	28.9 ± 24.9	37.5 ± 32.1	38.1 ± 26.1
Patients requiring defibrillation (%)	77.4	70.3	75	70.0
Lignocaine (mg)	87.3 ± 20.5	95.0 ± 12.3	115.8 ± 37.8	122.7 ± 53.6
Phenylephrine (mg)	4.9 ± 4.8	7.5 ± 6.4	7.5 ± 5.4	13.1* ± 18.5
Mg^{++} (mmol/l)				
Before CPB	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.2	0.8 ± 0.1
After CPB	2.0¶ ± 0.4	2.3§¶ ± 0.6	2.6‡¶ ± 0.5	2.8†¶ 0.6
CK-MB (%)				
Before CPB	2.28 ± 1.4	2.5 ± 2.5	2.1 ± 1.2	2.4 ± 1.8
After CPB	2.6 ± 2.9	3.2 ± 3.1	3.4 ± 2.6	2.5 ± 1.9

CPB = cardiopulmonary bypass.
* 6 g differs from 2 g and 4 g groups.
†6 g differs from 0 and 2 g groups.
‡4 g differs from 0 g group.
§2 g differs from 0 g group.
¶Before CPB differs from after CPB ($P < 0.001$).

tion (mmol/l); (*x*) CK-MB fraction (%); (*xi*) dobutamine before and after bypass (μg/kg/min); (*xii*) nitroglycerin required before and after bypass (μg/kg/min); (*xiii*) adrenaline required before and after bypass (μg/kg/min); and (*xiv*) new Q-waves on a postoperative ECG recorded 24 hours after bypass.

Protocol

Patients were randomly assigned to receive 0, 2, 4 or 6 g magnesium sulphate, which was slowly infused from after the induction of anaesthesia and completed at the time the aortic cross-clamp was removed.

If ventricular tachycardia or fibrillation occurred after removal of the aortic cross-clamp, the heart was directly defibrillated with the following energy sequence: 10, 10, 15, 15, 20 joules (J). If ventricular fibrillation persisted after the second 15 J defibrillation, lignocaine was administered into the pump (1 mg/kg). During reperfusion the coronary perfusion pressure was maintained with the previously specified range.

Measurements were taken before anaesthesia, before heparinisation, after bypass and completion of the protamine sulfate, and 12 hours after bypass.

CK-MB fraction was only measured before anaesthesia and 24 hours after bypass.

Analysis of data

Data were analysed with one-way analysis of variance (ANOVA) and subsequent multiple comparisons were performed with the Student-Newman-Keuls test. Proportions were compared with the chi-squared test. If the data were not normally distributed, the Mann-Whitney rank sum non-parametric test was performed. A *P*-value of < 0.05 was accepted as indication of significant differences between variables.

Results

Data from 138 patients could be used for analysis. The demographics are summarised in Table I. Significant differences between groups included the proportion of men to women, with more women in the 4 g $MgSO_4$ group. There was also a higher incidence of orthopnoea and paroxysmal nocturnal dyspnoea in the 4 g and 6 g $MgSO_4$ groups. However, the incidence of cardiac failure on pre-operative examination was similar between groups.

Table II shows the cardiopulmonary bypass and aortic cross-clamp times that were similar between groups. The incidence and amount of joules required for defibrillation once the aortic cross-clamp was taken off were similar between groups. The blood concentration for magnesium was higher at the time the aortic cross-clamp was released in the magnesium groups when compared with their own initial value. There were small but significant differences between final magnesium values attained as the dose of magnesium was increased.

The haemodynamics for the various groups and steps are summarised in Table III. In the control group the heart rate increased after the initial measurements were taken, while

TABLE III. HAEMODYNAMIC VALUES AND DRUGS REQUIRED FOR CIRCULATORY SUPPORT (MEAN ± SD)

$MgSO_4$	Step	HR (b/min)	SAP (mmHg)	DAP (mmHg)	CVP (mmHg)	Dob (μg/kg/min)	Adr (μg/kg/min)	TNT (μg/kg/min)
	1	64 ± 15	142 ± 26	75 ± 12	8 ± 3	3.5 ± 1.8	0	0.7 ± 0.3
0 g	2	92 ± 15*	116 ± 17*	65 ± 9*†	10 ± 6.4*	9.3 ± 6.4*	0.2 ± 0.2*	1.3 ± 0.9
(N = 31)	3	94 ± 13*	121 ± 16*	62 ± 9*	10 ± 3*	8.0 ± 3.3*	0.2 ± 0.2*	0.9 ± 1.0
	4	90 ± 12*	127 ± 15*	64 ± 11*	10 ± 3*	8.3 ± 6.3	0.1 ± 0.1	0.9 ± 0.9
	1	69 ± 12	134 ± 24	76 ± 19	8 ± 4	3 ± 0	0.01 ± 0	1.5 ± 2.6
2 g	2	92 ± 15*	111 ± 11*	59 ± 7*	10 ± 4*	8.0 ± 5.0	0.4 ± 1.1	1.5 ± 1.7
(N = 37)	3	99 ± 13*	120 ± 14*	63 ± 8*	11 ± 4*	6.9 ± 4.2	0.2 ± 0.4	0.6 ± 0.7
	4	98 ± 15*	128 ± 15	68 ± 14*	10 ± 3*	6.0 ± 3.0	0.2 ± 0.6	0.7 ± 0.7
	1	70 ± 13	140 ± 20	7 ± 11	9 ± 4	4.7 ± 3.0	0.03 ± 0.1	0.5 ± 0.3
4 g	2	97 ± 15*	118 ± 17*	60 ± 9*	11 ± 4*	10.5 ± 3.5*	0.4 ± 1.1	1.3 ± 1.3*
(N = 40)	3	94 ± 12*	120 ± 12*	60 ± 11*	11 ± 4	9.9 ± 4*	0.13 ± 0.1	1.1 ± 1.7*
	4	94 ± 15*	126 ± 12*	67 ± 12*	12 ± 5*	7.7 ± 5.8*	0.1 ± 0.1	1.9 ± 5.1*
	1	64 ± 12	137 ± 21	77 ± 11	9 ± 5	0	0	0.8 ± 0.3
6 g	2	92 ± 14*	120 ± 13*	62 ± 8*	10 ± 4	102 ± 5.5*	0.2 ± 0.2*	0.9 ± 0.8*
(N = 30)	3	94 ± 14*	115 ± 13*	59 ± 7*	11 ± 4	10.7 ± 4.8*	0.2 ± 0.1*	0.5 ± 0.4*
	4	98 ± 15*	128 ± 15	66 ± 11*	11 ± 4	7 ± 4.2*	0.1 ± 0.1*	0.7 ± 0.7*

HR = heart rate; SAP, DAP = systolic and diastolic arterial pressure; CVP = central venous pressure; Dob = dobutamine; Adr = adrenaline; TNT = nitroglycerin.
* Compares the designated value with its own step 1.
†Compares the designated value with similar steps of 2 g and 4 g $MgSO_4$ groups.

the blood pressure decreased after induction of anaesthesia and remained less than control for the rest of the experiment. The CVP increased once anaesthesia was induced and ventilation was started. There was an increase in the dobutamine and adrenaline requirements after cardiopulmonary bypass. A similar pattern was noted for the other three groups.

Significantly more phenylephrine was required for the patients who received 6 g $MgSO_4$ when compared with the other three groups.

The CK-MB fraction did not increase from the before to after values in any of the groups, and the groups did not differ from one another. The incidence of new Q-waves on the ECG after CABG did not differ between groups.

Discussion

The protocol used in this model failed to demonstrate any beneficial effects of magnesium on reperfusion injury of the heart. This is at variance with the theory of the reperfusion injury,[2,3] animal experiments[5,9,10,14] and some clinical studies.[15,16]

Published reports suggest that intracellular calcium overload is an important factor, and probably the final common pathway in causing the reperfusion injury.[3,17] Some authors[1,2] suggest that free oxygen radical formation precedes the calcium overload, while other data appear to differ. Meissner and Morgan[18] demonstrated an early increase in intracellular calcium, while Jeremy *et al.*[19] demonstrated peak calcium contractions at approximately 5 minutes after reperfusion is started. Thereafter the intracellular calcium concentration subsided to a level somewhat in excess of the normal intracellular calcium concentration.[6] Drugs that attenuate the radical formation or intracellular calcium overload lessen the extent of the reperfusion injury.[5,7]

Magnesium is a physiological calcium antagonist;[8] our hypothesis was, therefore, that magnesium will reduce the reperfusion injury. The hypothesis was further supported by data from animal experiments that clearly demonstrated beneficial effects when additional magnesium was administered,[9] while a chronic depletion of magnesium resulted in an exaggerated reperfusion injury.[10] Our own experimental data in a porcine model showed that the administration of magnesium (30 mg/kg) immediately before the release of a 15-minute occlusion of the left anterior descending (LAD) artery, resulted in less ventricular arrhythmias and a rapid recovery of systolic myocardial function.[11]

Clinical studies are, however, less clear on the issue of magnesium after myocardial infarction. The LIMIT-2 trial[12] reported an improved outcome if magnesium was administered to patients after they suffered a myocardial infarction. These results could not be confirmed in the ISIS 4 study.[13] It should, however, be noted that these studies were performed in a different setting compared with the present study. The LIMIT and ISIS trials gave magnesium to patients some time *after* myocardial infarction, while we gave magnesium *before* reperfusion was started.

Although the pre-operative (chronic) ischaemic burden between our experimental groups could have varied, we hypothesised that the real ischaemic insult was the application of the aortic cross-clamp. The cross-clamp times between our groups were similar and we therefore speculate that the degree of myocardial ischaemia, and hence the reperfusion injury, was similar in the four study groups. In addition, we gave the magnesium before the start of the reperfusion in order to have the maximum possible benefit early in the reperfusion time.

There are a number of possible explanations for our failure to show any advantage to the administration of magnesium.

1. There is no real benefit. Our data were collected in a randomised prospective fashion and although the clinician collecting the data was not blinded, the principal author was unaware of the groups to which the patients were allocated. The ischaemic insult (with reference to aortic cross-clamp

times) was similar, and the management of the haemodynamics was similar between the clinicians. Power analyses of some of the key results suggest that the number of patients included was sufficient for an alpha = 0.05 (varying from 70% to > 99%, with the lowest values obtained from adrenaline and dobutamine infusions). From this we have to conclude that there is no difference in the results and that we failed to confirm the hypothesis with our study protocol.

2. The methods employed to detect the reperfusion injury are not sufficiently sensitive to detect stunning. Stunning primarily refers to systolic dysfunction, i.e. poor myocardial contractility.[20] This is best detected with echocardiography. We relied on general haemodynamic parameters and the use of vaso-active drugs required to restore the circulation to predetermined endpoints. However this approach is nonspecific and will not demonstrate small differences. In retrospect, this must be regarded as a major limitation in our methodology.

However, reperfusion arrhythmias could be detected reliably and we failed to demonstrate a difference in the incidence or severity of arrhythmias. From this perspective we again conclude that the hypothesis was not confirmed, i.e. that the magnesium given in this protocol did not affect the reperfusion injury. If the arrhythmias were not significantly affected by the magnesium it is unlikely that the stunning will behave in a different manner.

3. The blood concentration of the magnesium was not sufficient to have an effect. We used doses similar to those used in previous studies. The LIMIT-2 trial[12] gave an intravenous bolus of 2 g followed by approximately 0.7 mmol per hour. Iseri[21] reports on the use of 2 g bolus and 0.5 g per hour thereafter, while the ISIS-4 study[13] used a 2 g bolus and 0.75 g per hour thereafter up to 24 hours. Another clinical study[22] utilised 6 g over 3 hours followed by 10 g over the next 21 hours, while a meta-analysis reports an average administration of 0.5 g per hour.[23] Our maximum rate of administration was 0.5 g per hour for the 6 g group.

Our aim was to elevate the blood concentration of magnesium so that at the time the aortic cross-clamp was removed we could study the effect of various blood concentrations of magnesium on the reperfusion injury. Although we achieved a dose-dependent increase in magnesium blood concentrations, the differences between groups were rather small.

It is possible that the absence of a more pronounced increase in the magnesium concentration can be explained by the large volume of distribution for magnesium coupled with the rapid renal excretion of the ion. James[24] suggests that in order to increase the level of magnesium significantly a large initial bolus be given (40 - 60 mg/kg), followed by a continuous infusion of 15 - 30 mg/kg/h.

However, further increase in blood concentrations may not be warranted in the peri-operative period as there is a potential risk of poor myocardial function and/or conduction disturbance after hypothermia, cardioplegia and cardiac surgery. Accordingly we did not think it would be ethically justifiable to use higher doses of magnesium for a clinical study in these particular settings.

What was unexpected, however, was the fact that the group that did not receive magnesium demonstrated an increase in magnesium blood concentration once the aortic cross-clamp was removed. Previous studies have shown that magnesium concentration decreases after cardiopulmonary bypass (CPB), probably owing to acute haemodilution caused by the clear prime of the CPB circuit.[25,26] The most probable explanation for the increase in the group not receiving magnesium is the use of the St Thomas solution, which contains a significant concentration of magnesium. This explanation is supported by a study conducted by Manners and Nielsen[27] who also showed an increase in magnesium concentration after bypass when St Thomas solution was used. The increase they reported was, however, smaller than that which we have shown and the difference may well be ascribed to a difference in the volumes of cardioplegia used. They only infused cardioplegia 45 minutes after initial arrest, while we used cardioplegia every 15 - 20 minutes.

4. An alternative, although improbable, explanation for our failure to confirm our hypothesis may be that the myocardial protection in our groups was such that there was little myocardial ischaemia and hence only an insignificant degree of reperfusion injury. The liberal use of beta-adrenergic blockers, halothane, arresting the heart in diastole, proper venting of the left ventricle, hypothermia and the use of oxygenated cardioplegia all contribute towards effective myocardial protection.[28] However, the fact that a significant number of patients had reperfusion arrhythmias and that the inotropic requirements post-CPB were higher than those used before CPB, argue against the absence of a reperfusion injury.

5. St Thomas cardioplegic solution contains a significant amount of magnesium. With the liberal use of cardioplegia the myocardial intra- and extracellular magnesium could have attained a supranormal value and exerted a maximum protective effect — hence the failure to demonstrate any beneficial effects from additional magnesium as administered in our protocol.

6. The model we used for this study, i.e. aortic cross-clamp, may not be appropriate. A number of drugs were used, there was variation in the duration of cross-clamp, and the quality of the surgical reperfusion varied. In addition, there was a significant number of new Q-waves recorded, i.e. indicating cell death. However, because aortic cross-clamping invariably causes some degree of ischaemia, and because the incidence of Q-waves as well as other variable factors was equally distributed between groups, we think that the model and the comparison are indeed valid.

In conclusion, we failed to demonstrate beneficial effects of additional magnesium before the release of the aortic cross-clamp during cardiac surgery. A higher blood concentration of magnesium than that which we attained may well be required to demonstrate beneficial effects. However, because of the possible negative effects on cardiac performance in the circumstances of cardiac surgery, this may well be the limitation of magnesium as a therapeutic option in this particular scenario.

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